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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/841,951	04/25/2001	Amos B. Smith III	4730-103 US	6213
25241	7590	11/26/2003		
MATHEWS, COLLINS, SHEPHERD & GOULD, PA 100 THANET CR, SUITE 306 PRINCETON, NJ 08540				
			EXAMINER EPPERSON, JON D	
			ART UNIT 1639	PAPER NUMBER 10
DATE MAILED: 11/26/2003				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary*File Copy***Application No.**

09/841,951

Applicant(s)

SMITH ET AL.

Examiner

Jon D Epperson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 April 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-15 is/are pending in the application.
- 4a) Of the above claim(s) 8-15 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 6) ☐ Other: _____

DETAILED ACTION

Status of the Application

1. Receipt is acknowledged of a Response to a Restriction Requirement, which was dated on April 17, 2003 (Paper No. 9).

Priority Claims

2. The priority filing date of April 26, 2000 for 60/200,022 is acknowledged.

Status of the Claims

3. Claims 1-15 were pending in the present application.
4. Applicants' responses to the Restriction and/or Election of Species requirements in Paper Nos. 7 and 9 are acknowledged (Applicant elected Group I, i.e., claims 1-7) and claims 8-15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim (see *Response to Restriction and/or Election of Species requirement* below). The Examiner further notes that claim 1 contains reference to solid-phase synthesis methods and as such is withdrawn in part i.e., the part that states R7 is a solid support (e.g., see claim 1, step (a)).
5. Therefore, claims 1 (in part) and 2-7 are examined on the merits in this action.

Response to Restriction and/or Election of Species

6. Applicant's election of Group I (claims 1-7) in Paper No. 7 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a) and/ or 37 CFR 1.111(b)).

7. Applicant's election of species in Paper Nos. 7 and 9 is also acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election of species has also been treated as an election without traverse (MPEP § 818.03(a) and/ or 37 CFR 1.111(b)).

8. As a result, the restriction requirement and/or election of species is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

9. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98 (b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless

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the references have been cited by the examiner on the form PTO-892, they have not been considered.

10. The references listed on applicant's PTO-1449 form have been considered by the Examiner. A copy of the form is attached to this Office Action.

Specification

11. Applicant has not given a post office address anywhere in the application papers as required by 37 CFR 1.33(a), which was in effect at the time of filing of the oath or declaration. A statement over applicant's signature providing a complete post office address is required.

12. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claims Rejections - 35 U.S.C. 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claim 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of preparing polypyrrolinones having formula **38** (shown in claim 1) using potassium hexamethyldisilazane (KHMDs) to promote the cyclizing step (see

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claim 1 (b)) and Swern Oxidation to convert the primary alcohol **41** into the corresponding aldehyde (see, claim 1 (c); see also Examples), the specification does not reasonably provide enablement for a method using any base for cyclization (especially for the production of diastomerically pure polypyrrolinones) or the use of any oxidation steps (especially since these compounds are susceptible to degradation under harsher oxidation conditions, see below). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims. This is an enablement rejection.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". Some of these factors may include, but are not limited to:

- (1) the breadth of the claims;
- (2) the nature of the invention;
- (3) the state of the prior art;
- (4) the level of one of ordinary skill;
- (5) the level of predictability in the art;
- (6) the amount of direction provided by the inventor;
- (7) the existence of working examples; and
- (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) The breadth of the claims and the nature of the invention: The claims are drawn to a three-step iterative synthesis for polypyrrolinones which includes steps for (a) immine formation, (b) cyclization and (c) oxidation. The scope of the claims is broad because the reagents for these three steps are not specified and, as a result, potentially an infinite

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number of possibilities exist. Consequently, the nature of the invention cannot be determined in light of the foregoing i.e., without knowledge of the specific reagents being used in the method.

(3 and 5) The state of the prior art and the level of predictability in the art: The prior art teaches that bases other than KHMDS used for cyclization in step (b) of claim 1 do not work (e.g., see Smith A. B.; Liu, H.; Hirschmann, R. "A Second-Generation Synthesis of Polypyrrolinone Nonpeptidomimetics: Prelude to the Synthesis of Polypyrrolinones on Solid Support" Organic Letters 2000, 2, 14, 2037-3040, page 2039, paragraph 2, "Interestingly, other amide bases, such as LDA, LTMP, and LiHMDS, led to unsaturated lactam (-) 20 as a major side product"). The Examiner contends that a wide variation in product yield even for bases that are almost identical (e.g., compare KHMDS versus LiHMDS) clearly demonstrates the "unpredictable" nature of the cyclization reaction and/or its inherent limitations. In addition, the Examiner sets forth Gung et al (see Gung, B. W.; Francis, M. B. "Diastereofacial Selectivity in Intramolecular 1,4-Conjugate Additions: Conclusive Evidence for the Importance of Ground-State Conformations and the σ^* Orbital Effect" J. Org. Chem. 1993, 58, 6177-6179, especially Table 1 showing large differences in stereoselectivity obtained for similar HMDS cyclization reactions), which shows that an additional layer of unpredictability is added to this reaction when "diastereomerically pure" compounds are required (e.g., see claim 2).

Furthermore, the prior art also teaches that mild oxidation reagents like Swern oxidation must be used (e.g., see Smith A. B.; Liu, H.; Hirschmann, R. "A Second-Generation Synthesis of Polypyrrolinone Nonpeptidomimetics: Prelude to the Synthesis

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of Polypyrrolinones on Solid Support” Organic Letters 2000, 2, 14, 2037-3040, page 2039, Table 1). The Examiner notes that Smith et al stated that even for the same Swern reactions “the choice of base proved crucial” (e.g., see Smith et al, page 2039, paragraph bridging columns 1 and 2). The Examiner also notes that other reagents led to decomposition (e.g., see entry 4 in Table 1) and that stronger reagents like powerful transition metal oxidants would almost certainly destroy these compounds (e.g., see Carey, F. A. and Sundberg, R. J. Advanced Organic chemistry Third Edition Part B. 1990: Plenum Press. 1990, pages 620-621 comparing the use of strong oxidation reagents like transitional metal complexes to the use of DMSO in conjunction with various reagents including oxalyl chloride i.e., the Swern oxidation).

(4) The level of one of ordinary skill: The level of skill would be high, most likely at the Ph.D. level.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants specification teaches only KHMDS and Swern oxidation using a limited number of bases including DBU and di-iso-propylethyl amine (e.g., see Examples; see also claims 4-7).

(8) The quantity of experimentation needed to make or use the invention base on the content of the disclosure: The inventor provides no guidance beyond the aforementioned Examples taught in the specification. As a result, one of ordinary skill in the art could not predict what other types of compounds could effectively be synthesized via methods of the claimed invention and, consequently, an indeterminate quantity of experimentation would be necessary to synthesize “all” possible compounds on a “high

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load” Merrifield Resin. There must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 & n.23 (Fed. Cir. 1991). Therefore, it is deemed that further research of an unpredictable nature would be necessary to make or use the invention as claimed. Thus, due to the inadequacies of the instant disclosure one of ordinary skill would not have a reasonable expectation of success and the practice of the full scope of the invention would require undue experimentation.

Claims Rejections - 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. For **claims 1 and 3**, the term “lower” as used in conjunction with “alkyl” or “alkoxy”, etc. is vague and indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. See also MPEP § 2173.05(b). Applicants are requested to clarify. Therefore, claims 1 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

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B. **Claim 1** recites improper Markush format. For example, claim 1 recites, "R is independently selected from a group consisting of a straight C1-C6 alkyl ... or cyano ... or heteroaryl." The term "or" must only be used once and the phrase "selected from the group consisting of" is also proper as outlined below. It is suggested to use standard Markush language; see MPEP 2173.05(h) concerning alternative expressions:

Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. One acceptable form of alternative expression, which is commonly referred to as a Markush group, recites members as being "selected from the group consisting of A, B and C." See *Ex parte Markush*, 1925 C.D. 126 (Comm'r Pat. 1925).

When materials recited in a claim are so related as to constitute a proper Markush group, they may be recited in the conventional manner, or alternatively. For example, if "wherein R is a material selected from the group consisting of A, B, C and D" is a proper limitation, then "wherein R is A, B, C or D" shall also be considered proper.

Therefore, claims 1 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

C. For **claim 1**, the term "exposing" as used in the cited method steps is vague and indefinite. For example, the Examiner contends that if the term "exposing" means anything other than "reacting" then the cited method steps will not work. Applicants are requested to clarify and/or correct. Therefore, claims 1 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

D. For **claim 1**, the phrase "plurality of treatments" is vague and indefinite. The Examiner contends that it is not clear what the "other" treatments are? Consequently, the meters and bounds of the claimed limitations cannot be determined. Applicants are requested to clarify and/or correct. Therefore, claims 1 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

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E. **Claim 2** recites “substantially” diastereomerically pure in line 1. The term “large” is a relative term, which renders the claim indefinite and/or unclear. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. See also MPEP § 2173.05(b).

Contact Information

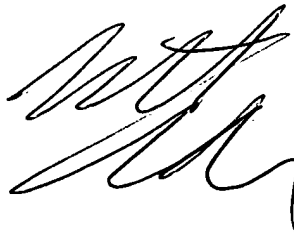
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (703) 308-2423. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (703) 306-3217. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-2439.

Jon D. Epperson, Ph.D.
November 15, 2003

BENNETT CELSA
PRIMARY EXAMINER

A handwritten signature in black ink, appearing to read 'Bennett Celsa', written over the printed name and title.